Electrochemical C(sp<sup>3</sup>)–H Fluorination

Yusuke Takahira<sup>a</sup>
Miao Chen<sup>a</sup>
Yu Kawamata<sup>a</sup>
Pavel Mykhailiuk<sup>b</sup>,<sup>c</sup>
Hugh Nakamura<sup>a</sup>
Byron K. Peters<sup>a</sup>
Solomon H. Reisberg<sup>a</sup>
Chao Li<sup>a</sup>
Longrui Chen<sup>c</sup>
Tomoyuki Shibuguchid<sup>d</sup>
Phil S. Baran<sup>a</sup>* 0000-0001-9193-9053

<sup>a</sup>Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
phar@scripps.edu
<sup>b</sup>Enamine Ltd., Chervonotkatska 78, 02094 Kyiv, Ukraine and Taras Shevchenko National University of Kyiv, Chemistry Department, Volodyymyrska 64, 01601 Kyiv, Ukraine
<sup>c</sup>Asymchem Life Science (Tianjin), Tianjin Economic-Technological Development Zone, Tianjin 300457, P. R of China
<sup>d</sup>Discovery, Medicine Creation, Neurology Business Group, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba-shi, Ibaraki, 300-2635, Japan

Published as part of the Cluster Electrochemical Synthesis and Catalysis

Received: 23.01.2019
Accepted after revision: 27.01.2019
Published online: 01.03.2019

Abstract A simple and robust method for electrochemical alkyl C–H fluorination is presented. Using a simple nitrate additive, a widely available fluorine source (Selectfluor), and carbon-based electrodes, a wide variety of activated and unactivated C–H bonds are converted into their C–F congeners. The scalability of the reaction is also demonstrated with a 100 gram preparation of fluorovaline.

Key words organic synthesis, electrochemistry, fluorination, C–H functionalization, radicals

Within the realm of synthetic organic electrochemistry, few applicable options exist for the C–H functionalization of unactivated aliphatic centers. In 2016 our lab reported a simple and inexpensive method for the oxidation of allylic C–H bonds featuring N-hydroxytetrachlorophthalimide as a mediator for hydrogen atom transfer. Shortly thereafter, it was found that the use of quinuclidine as mediator allowed for the oxidation of stronger C–H bonds such as unactivated methylenes. Based on requests from industrial collaborators in medicinal chemistry, we were compelled to extend this precedent to the problem of C–H fluorination. Although both photochemical and purely chemical means exist for accomplishing such a transformation (Scheme 1A), an electrochemical alternative was pursued to determine if there was any specific advantage in terms of scalability and/or selectivity. Disclosed herein is a practical and scalable approach to C(sp<sup>3</sup>)–H fluorination that utilizes Selectfluor in a unique way when coupled to anodic oxidation in the presence of a nitrate additive.

A truncated optimization table is depicted in Scheme 1B, wherein Selectfluor was chosen as a fluorine atom donor based on its wide availability. From a reactivity standpoint, one could also envisage three distinct roles for Selectfluor: as (1) its own electrolyte due to its ionic nature; (2) an electrophilic fluorine source; and (3) itself a mediator similar to quinuclidine. Using 1 as a model substrate, the impact of various reaction parameters was investigated (Scheme 1B). The fully optimized conditions called for the use of Selectfluor (3.0 equiv) and sodium nitrate (0.2 equiv) in acetonitrile with a pair of reticulated vitreous carbon (RVC) electrodes at 3 mA to deliver the desired fluorinated product 2 in 62% NMR yield (54% isolated, entry 1). Not surprisingly, the reaction was found to be sensitive to oxygen, as is rationalized from the proposed radical chain mechanism (vide infra, entry 2). The reaction was confirmed to be electrochemically driven and required a constant supply of current (entry 3). Extensive screening revealed that the sodium nitrate was essential for the initiation as well as for improving the reproducibility of this reaction (entries 4 and 5). The peculiar use of nitrate has precedent in the electrochemical literature; nitrate is known to be oxidized anodically to generate reactive radical species capable of abstracting hydrogen from substrates. The alternative fluorinating agent Selectfluor II (B) was also evaluated and did not improve the yield (entry 6). The likely role of Selectfluor as a mediator was supported by the fact that other electro-
phobic fluorinating sources (some known to capture nucleophilic radicals) failed to effect this transformation (entries 7 and 8).

The use of a Ni foam cathode instead of RVC had a deleterious effect upon this reaction (entry 9, for a detailed summary of electrodes screened, see the Supporting Information). Finally, increasing the current to 6 mA also resulted in lower yield (entry 10). In this case, the reaction resulted in incomplete conversion of the starting material with unidentified byproducts, likely due to the higher voltage.

With an optimized set of conditions in hand, the utility of electrochemical C–H fluorination was explored. The generality of this transformation is shown in Scheme 2, demonstrating efficient C–H fluorination on various classes of molecules including terpenes, amino acids and pharmaceutically relevant structures. Comparisons with chemical conditions available in the literature are also included in the Scheme 2. In general, fluorination occurs at the unactivated secondary or tertiary C–H bonds that are the most distal from the electron-withdrawing group. This regioselectivity tracks with innate reactivity towards an electrophilic oxidant and is reminiscent of the selectivity of electrochemical unactivated C–H oxidation, which strongly suggests that the C–H abstraction step proceeds via a mediated radical mechanism. Within the realm of secondary systems (Scheme 2A), simple acyclic and cyclic alkanes were fluorinated, including those bearing esters (3 and 4), ketones (5 and 6), and even alkyl bromides (8). In the case of sclareolide, the reaction gave a mixture of the corresponding fluorinated compounds 9 in 58% yield. Notably, even in the absence of sodium nitrate, 9 was obtained in 67% yield. Fluorination of tertiary systems generally proceeded in higher yield (Scheme 2B). Thus, acyclic, amino acid derivatives, and adamantanes were all fluorinated in synthetically useful yields. Fluorination of unsubstituted adamantanes generally led to a mixture of di-/tri-fluorinated products in reasonable yields, whereas high yields of mono-fluorination were observed when only one tertiary C–H bond was available (19 and 20). Access to fluorinated amino acids (12, 13, 17, and 18) is a promising application with known uses in drug discovery contexts. This methodology was also field-tested at Eisai where numerous building blocks were subjected to electrochemical fluorination and synthetically useful yields of valuable fluorinated products emerged (24, 25, and 26 in Scheme 2D). In order to demonstrate the simplicity with which this chemistry could be conducted on scale, a 100-gram scale fluorination of protected L-valine was provided the corresponding fluorinated adduct 12 in 78% yield (Scheme 2E) without significant erosion of enantiopurity (96% ee, see the Supporting Information). This was accomplished using a simple batch reactor (see the Supporting Information for details), but in principle could also be easily adopted to a flow setup.

Regarding the limitations of this method, several substrates delivered mixtures of isomers, showed no reaction, or decomposed under standard conditions (Scheme 2C). For example, C–H bonds adjacent to a heteroatom are prone to oxidation, resulting in degradation. No product formation but partial decomposition was observed in the case of strained systems such as the bicyclo[2.1.0]pentane framework 22 after passing a total charge of 1.0 F/mol at 1.5 mA under constant current conditions. Certain nucleophilic groups were not tolerated under the current conditions. Regardless of these limitations, the operational simplicity, reproducibility, and short reaction times are useful attributes of the present method. To further simplify the reaction conditions, it is worth noting that in the cases of sclareolide, adamantane, and the protected valine sodium nitrate was not required for efficient initiation of the reaction.

A proposed mechanism for electrochemical C–H fluorination is described in Scheme 3. Considering the fact that this reaction is a net redox-neutral transformation and that the regioselectivity is analogous to that of other radical-based C–H functionalizations, a radical chain mechanism is proposed. Initially, a small amount of organic radical is generated by either direct or nitrate-mediated electrochemical oxidation of a substrate. Subsequent fluorination by Selectfluor delivers radical cation 28, which can then abstract hydrogen from the substrate. Oxidative initiation was confirmed by conducting a reaction in a divided cell (without...
Y. Takahira et al.

Cluster

Synlett

2019, 30, 1178–1182

Cluster

Synlett

2019, 30, 1178–1182

Y. Takahira et al.

Cluster

Synlett

2019, 30, 1178–1182

nitrate), where reaction progress was observed only in the anodic chamber. Evidence for a radical chain reaction includes the observation of >100% current efficiency in the reaction shown in Scheme 4. The necessity of constant electricity supply for this radical chain process is not unusual because 28 can undergo nonproductive reaction pathways such as fragmentation and hydrogen abstraction from solvent or decomposed material.

We assume that the role of nitrate is to improve the efficiency of initiation, rather than as a chain carrier. This is supported by the fact that C–H fluorination of several substrates do not require a nitrate additive (vide supra), which clearly indicates that nitrate radical is not crucial for the reaction progress. In contrast, DABCO-containing fluorine sources are essential for successful reactions (see Scheme 1). Regarding the capability of nitrate as initiator, it is known that nitrate can be electrochemically oxidized.10 Cyclic voltammetry indicated that oxidation of nitrate indeed occurred at +2.2 V in acetonitrile with respect to Ag/AgCl reference electrode (see the Supporting Information).

Scheme 2 Electrochemical fluorination: Scope and applications
Thus, nitrate oxidation likely occurs before any direct anodic C–H abstraction.\textsuperscript{11} Taken together, it appears that (1) the nitrate additive is considered to be helpful in the initiation step; (2) Selectfluor-derived species (such as \textbf{28}) could participate in the propagation step as a chain carrier, though the efficiency of the propagation strongly depends on the substrate used. The triple utility of Selectfluor as a fluorine donor, mediator, and electrolyte is a rather memorable aspect of this chemistry.

Finally, as the mechanisms for electrochemical and photochemical C–H fluorinations are radical based, a small study was pursued to see if reactivity differences could be observed with different medicinally relevant scaffolds. As illustrated in Figure 1, substrates \textbf{24}, \textbf{25}, and \textbf{29} reacted quite differently and in all cases showed superior reactivity through the electrochemical mode. The origin of these differences is not clear but points to the need for complementary new approaches to achieve this valuable transformation.

In summary, a simple and scalable protocol for the electrochemical fluorination of unactivated C(sp\textsuperscript{3})–H bonds has been developed. The scope has been explored across a range of substrates bearing numerous types of functional groups and the ease of scale-up is evidenced by the 100-gram scale fluorination of a valine derivative. As electrochemical functionalization processes become more mainstream, it is likely that this method will find use alongside analogous C–H oxidation processes for both building-block diversification and metabolic prediction.

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{compound} & \textbf{photochem}\textsuperscript{a} & \textbf{electrochem}\textsuperscript{a} \\
\hline
\textbf{24} & 68% (H:F = ca. 10:7) & 78% (H:F = ca. 2:1) \\
\textbf{25} & 26%\textsuperscript{c} & 43% \\
\textbf{29} & 19%\textsuperscript{c} & 57% \\
\hline
\end{tabular}
\caption{Comparison of electrochemical and photochemical C–H fluorination using actual med-chem intermediates}
\end{table}

\section*{Funding Information}

Financial support for this work was provided by the NSF (#1740656), Pfizer, AGC Inc. (to Y.T.), Nankai University (to M.C.), the George E. Hewitt Foundation (to Y.K.), a Fulbright Scholar Fellowship (to P.M.), JSPS (to H.N.), the Swedish Research Council (VR 2017-00362 to B.K.P.), NSF GRFP (#2017237151) and a Donald and Delia Baxter Fellowship (to S.H.R.).

\section*{Acknowledgment}

The authors thank Dr. Jeremy T. Starr (Pfizer) for helpful discussions, Prof. A. L. Rheingold (UC San Diego) for X-ray crystallographic analysis, Dr. D.-H. Huang and Dr. L. Pasternack for assistance with NMR spectroscopy, Dr. J. Chen for assistance with HRMS and SFC analyses, and Dr. R. R. Merchant for assistance in the preparation of the manuscript. We thank Enamine Ltd. for providing samples of several substrates for fluorination, T.H. and T.S. would like to thank Mr. So Yasui for NMR data collection and support with compounds \textbf{24}, \textbf{25}, and \textbf{26}, Dr. Hikaru Yoshimura for supporting chemistry on this work, and Dr. Toshiki Kurokawa, Dr. Daiju Hasegawa, and Dr. Taro Terauchi for helpful discussions.

\section*{Supporting Information}

Supporting information for this article is available online at https://doi.org/10.1035/s-0037-1611737.

\section*{References and Notes}

Y. Takahira et al.


(7) General procedure for C(sp²)-H fluorination: To a 5 mL undivided ElectraSyn vial equipped with a stir bar was added substrate (0.30 mmol), Selectfluor (A) (3.0 equiv, 319 mg, 0.90 mmol), NaNO₃ (0.2 equiv, 5.1 mg, 0.06 mmol), and MeCN (3.0 mL). The vial cap equipped with a pair of RVC electrodes was screwed on, and the headspace of the vial was purged with Ar using a balloon, syringe and needle assembly prior to electrolysis. The reaction parameters of the ElectraSyn device were set up as follows: constant current, 3.0 mA; no reference electrode; total charge, 0.30 mmol substrate, ranging from 0.25 to 3.0 F/mol; alternate polarity, 2 min; stirring, 600 rpm. The mixture was electrolyzed under Ar atmosphere until complete or reasonable consumption of the starting material as judged by TLC. After electrolysis, the cap was removed, and the electrodes were taken out and rinsed with MeCN into the reaction mixture. The reaction mixture was poured into saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude material was purified by silica gel column chromatography or preparative thin-layer chromatography to furnish the desired product. See the Supporting Information for full details and graphical guide.


